Diabetes and Tuberculosis:
A Practical Approach to Diagnosis and Treatment

Michael Lauzardo, MD MSc

Chief, Division of Infectious Diseases and Global Medicine

Director, Southeastern National Tuberculosis Center
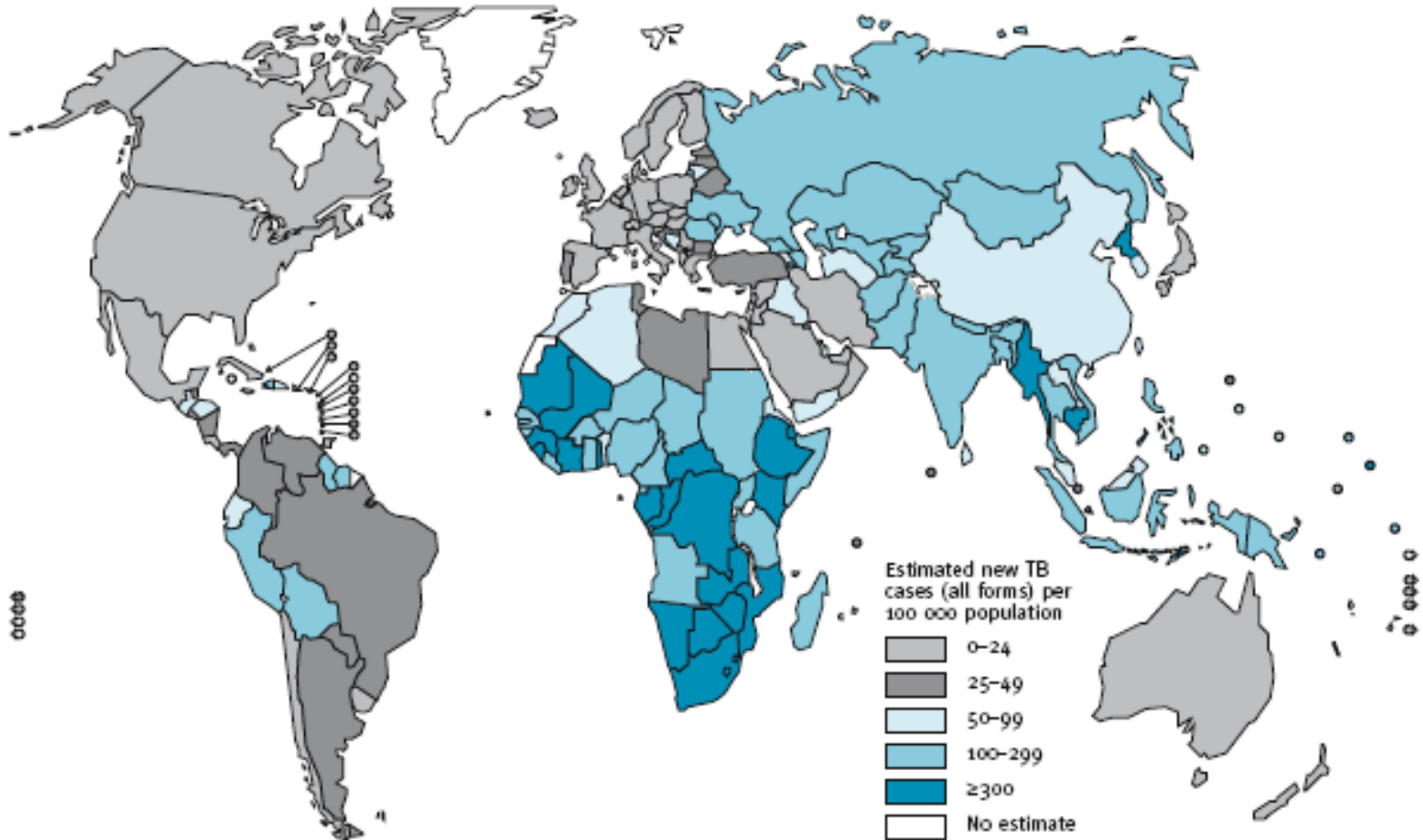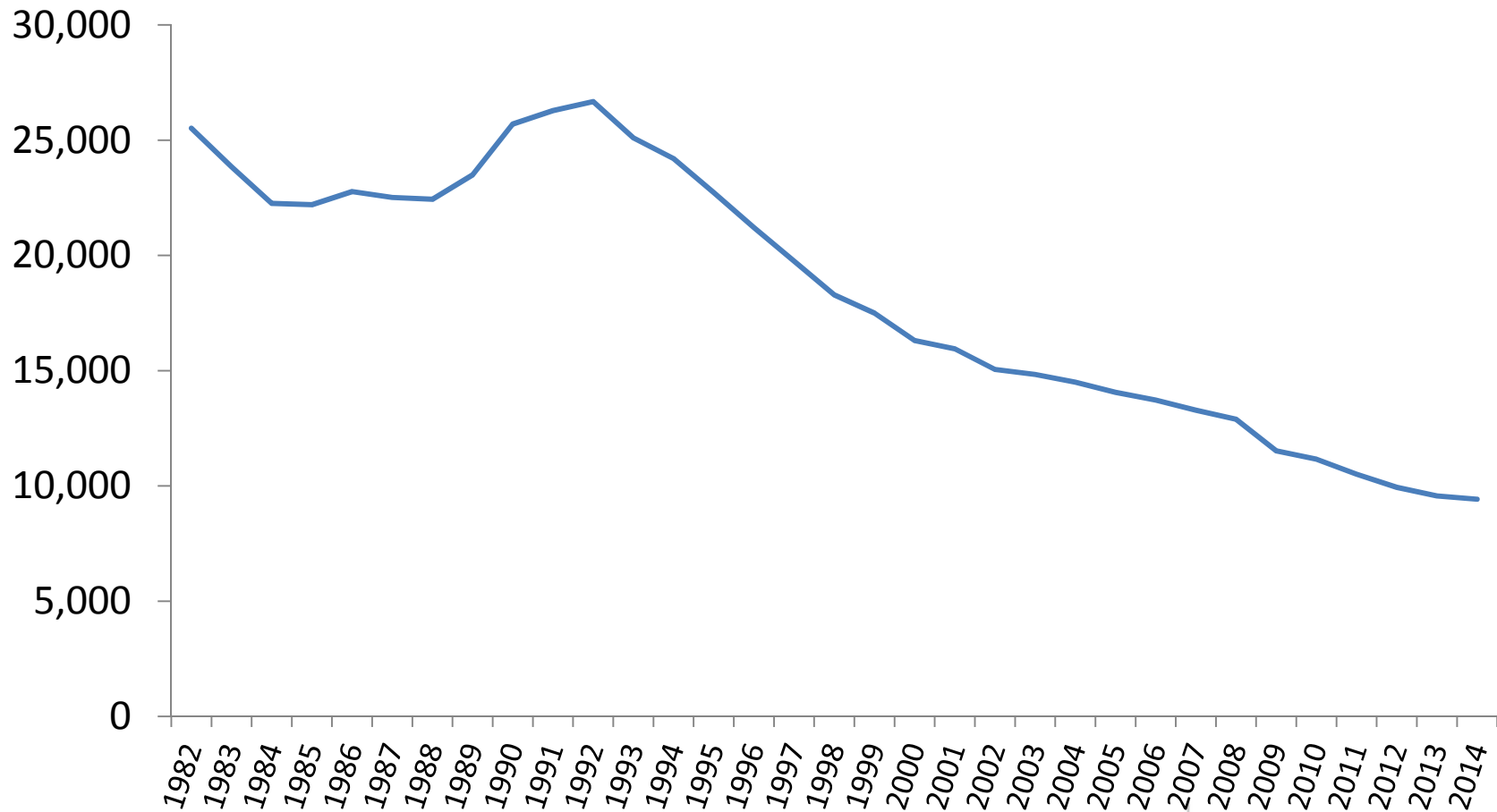
University of Florida

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Background

Epidemiology of Tuberculosis and Diabetes
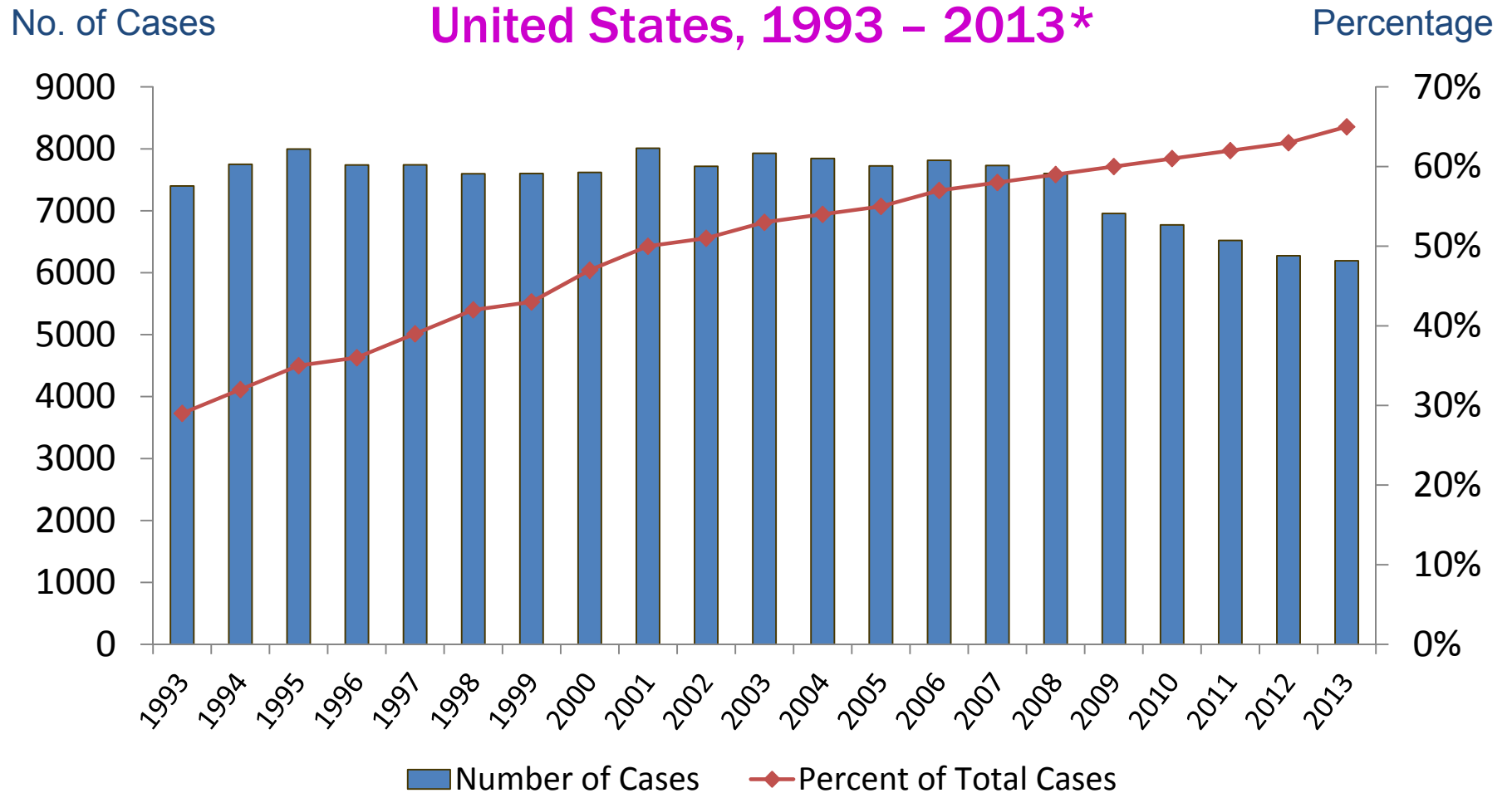
Estimated Tuberculosis Incidence
WHO

Estimated TB incidence rates, by country, 2009

Estimated new TB cases (all forms) per 100 000 population

- 0–24
- 25–49
- 50–99
- 100–299
- ≥300
- No estimate

Reported TB Cases
United States 1982-2014

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Trends in TB Cases in Foreign-born Persons,
United States, 1993 – 2013*

No. of Cases

Percentage

Legend: Number of Cases · Percent of Total Cases

*Updated as of June 11, 2014.

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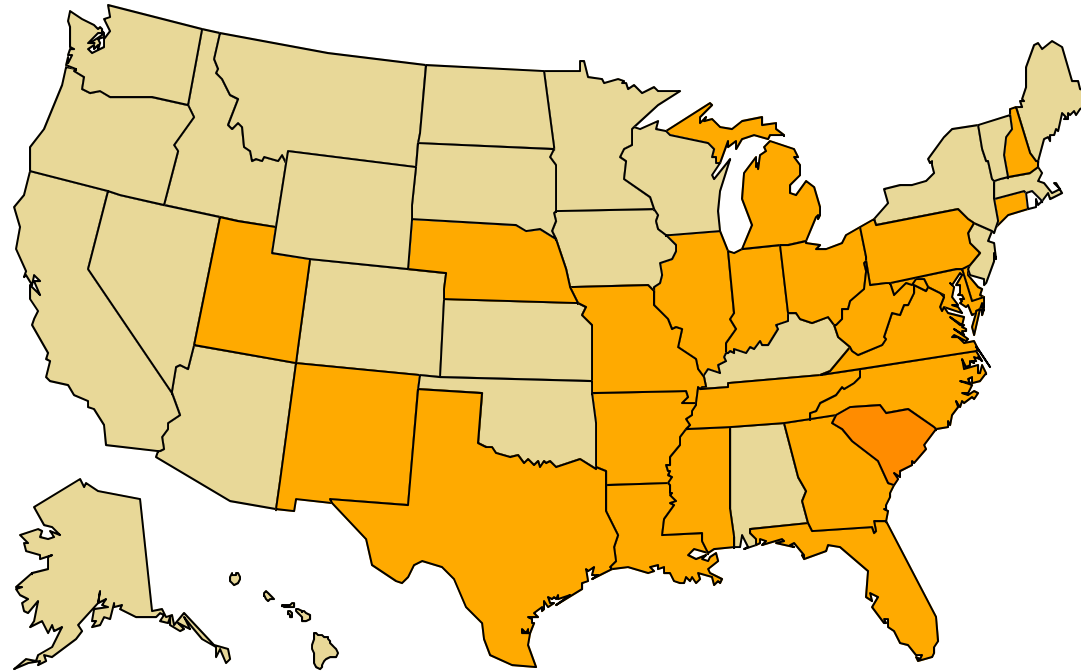
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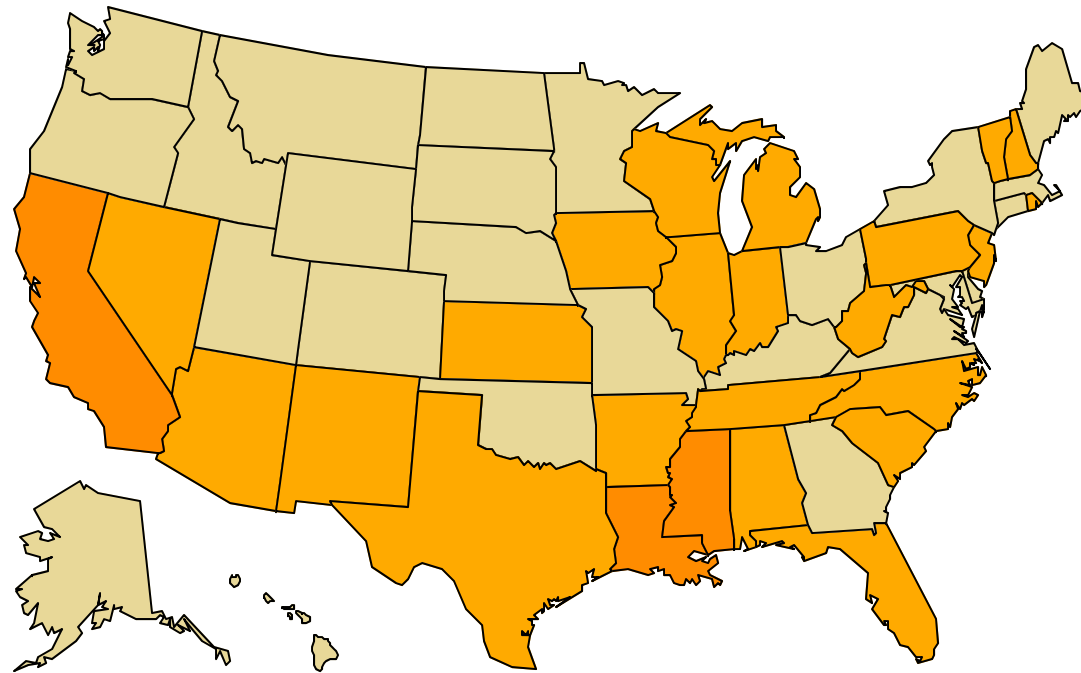
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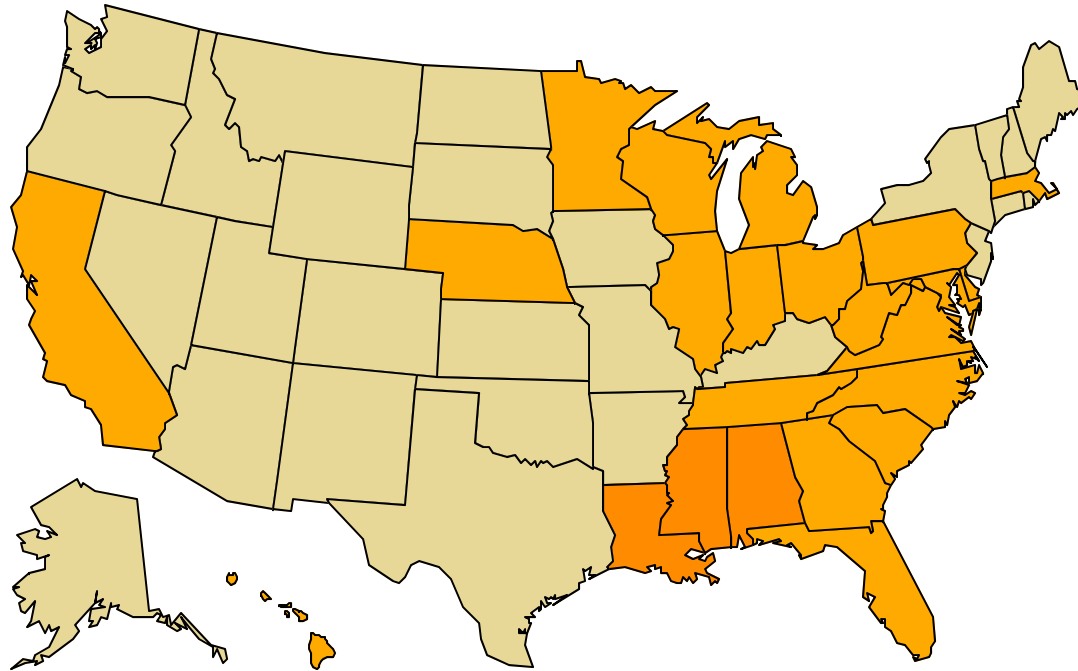
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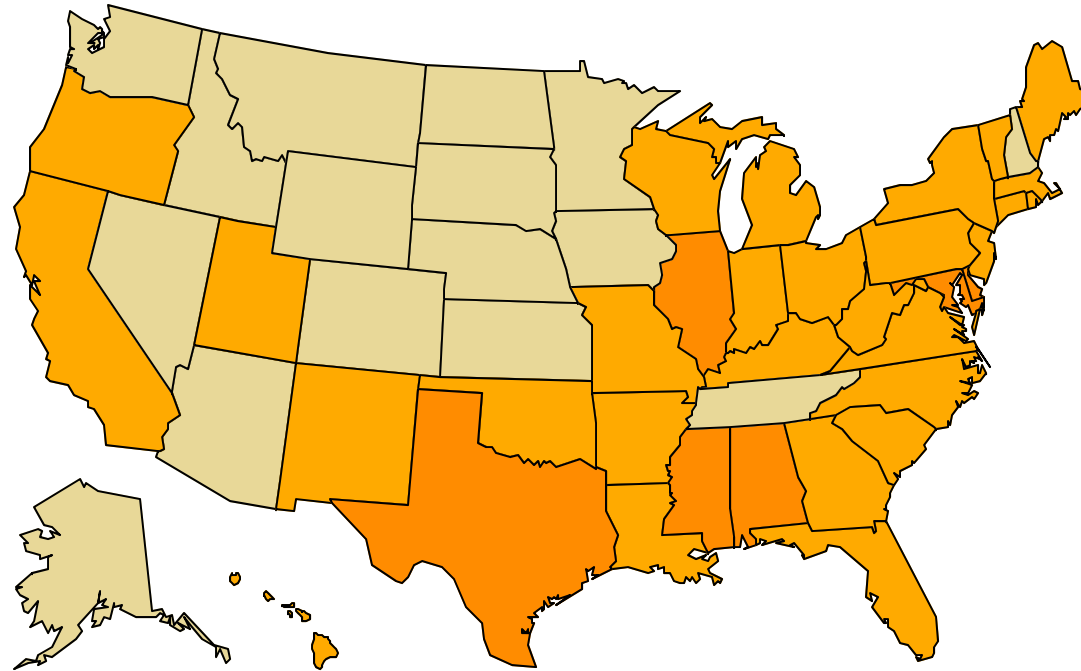
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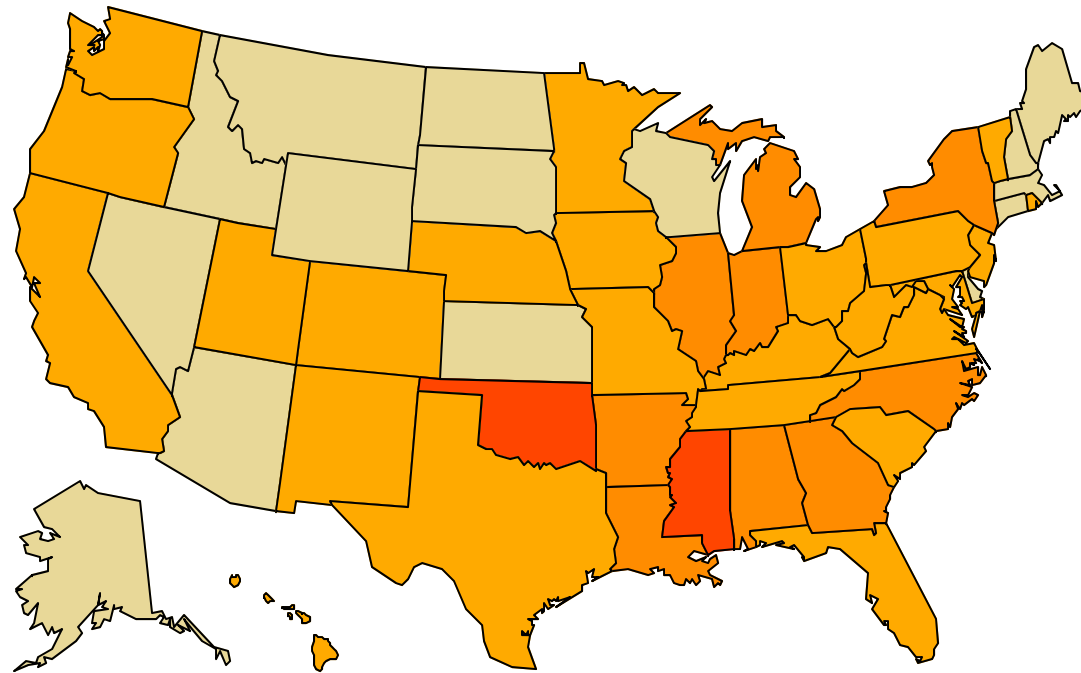
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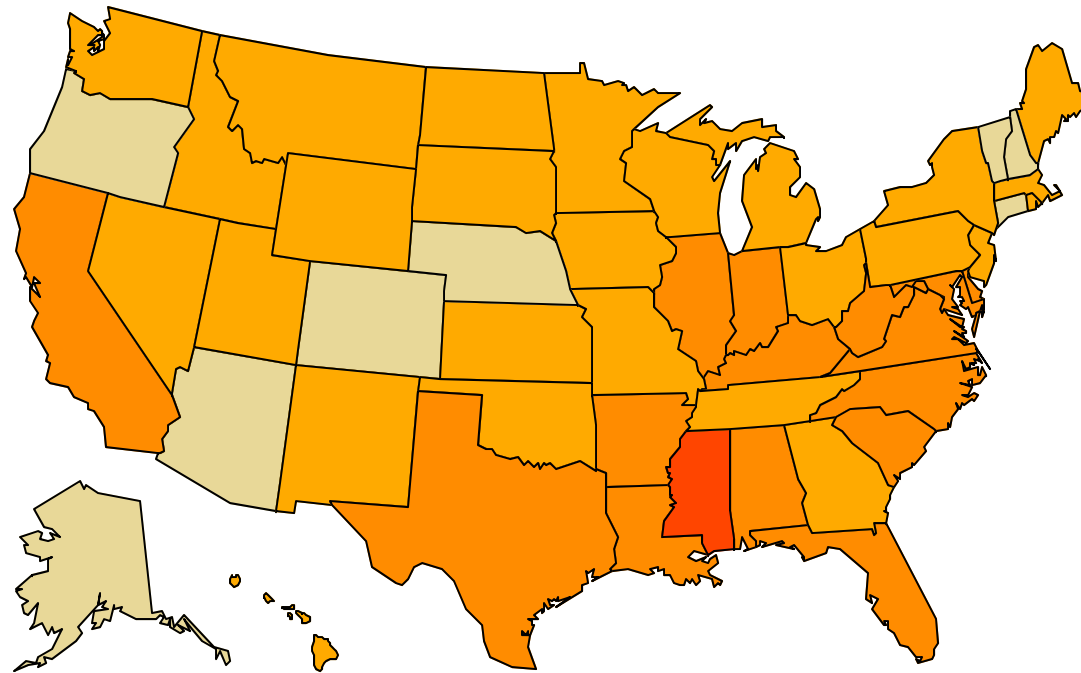
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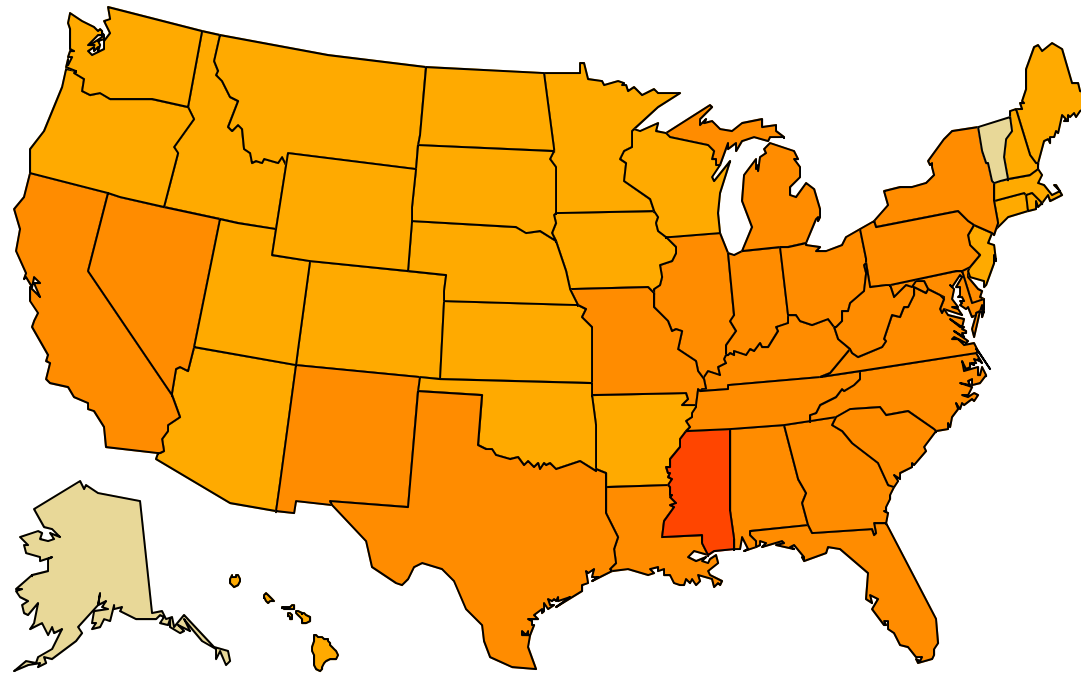
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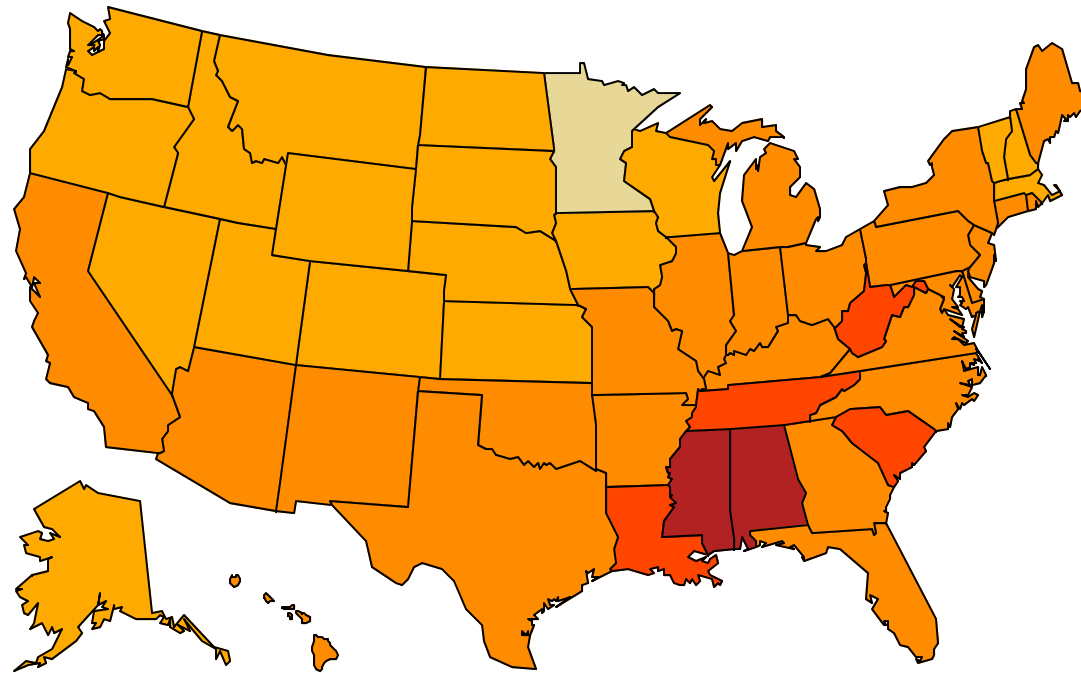
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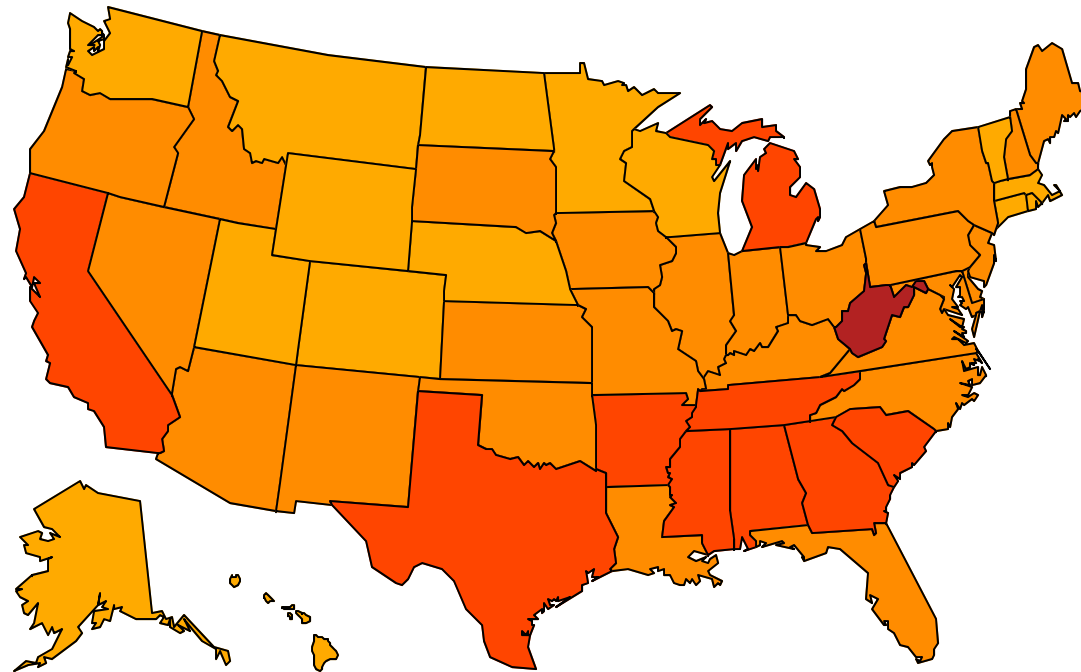
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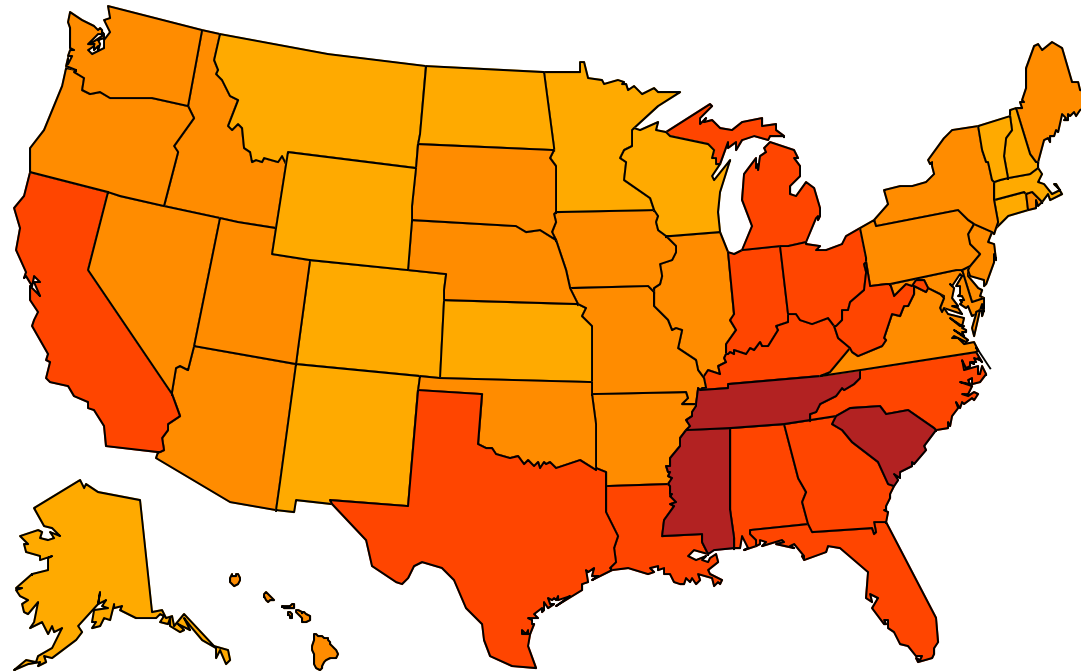
2004

2005

2006

2007

2008

2009

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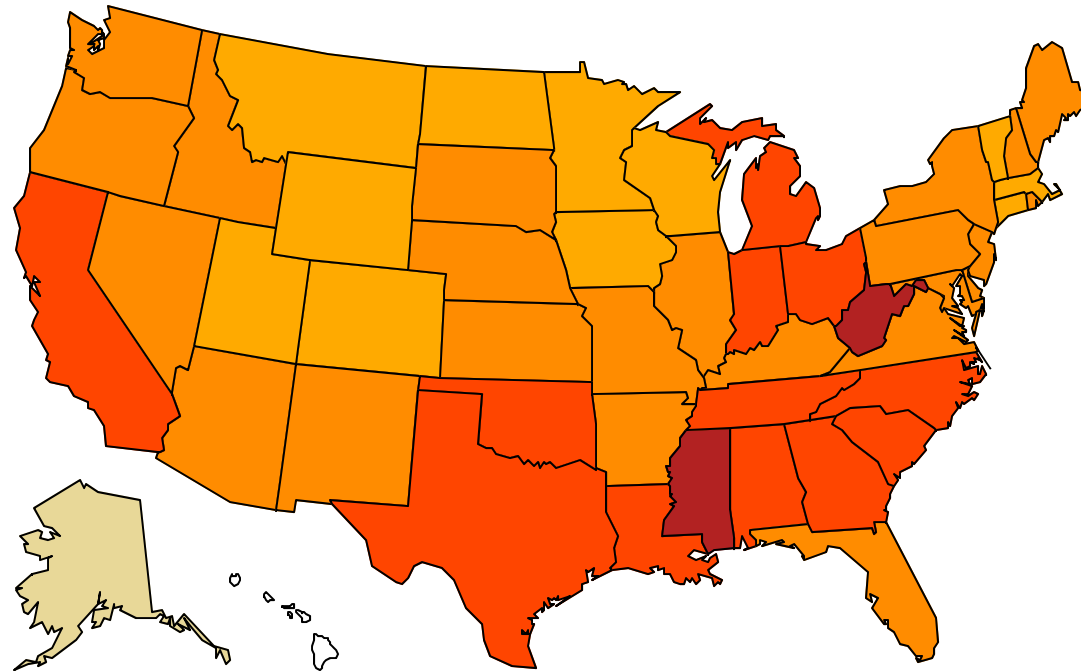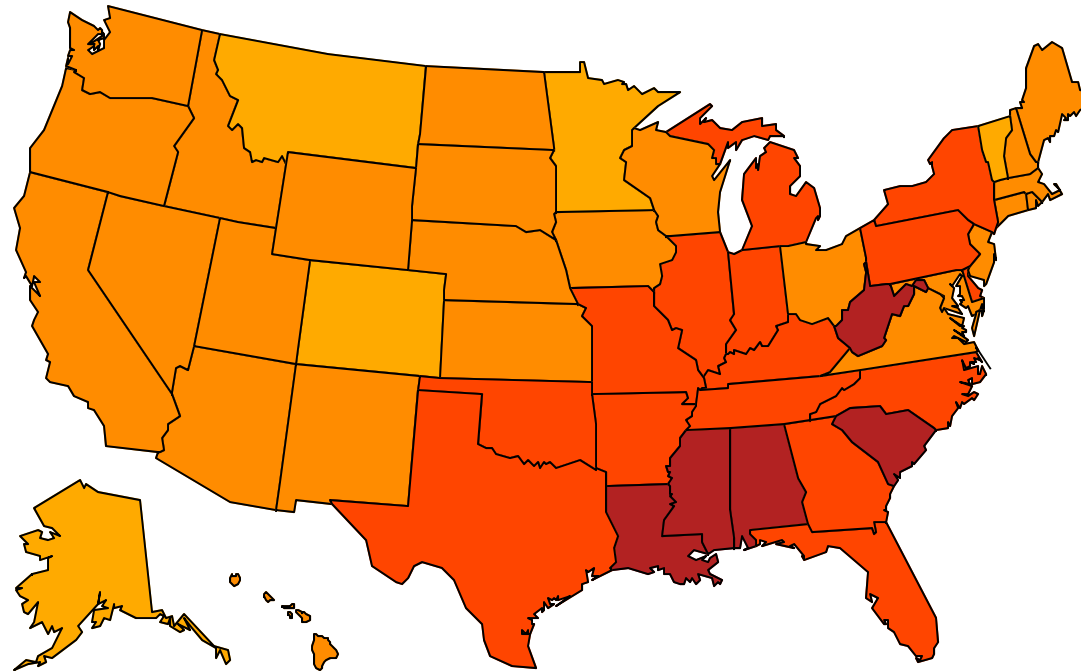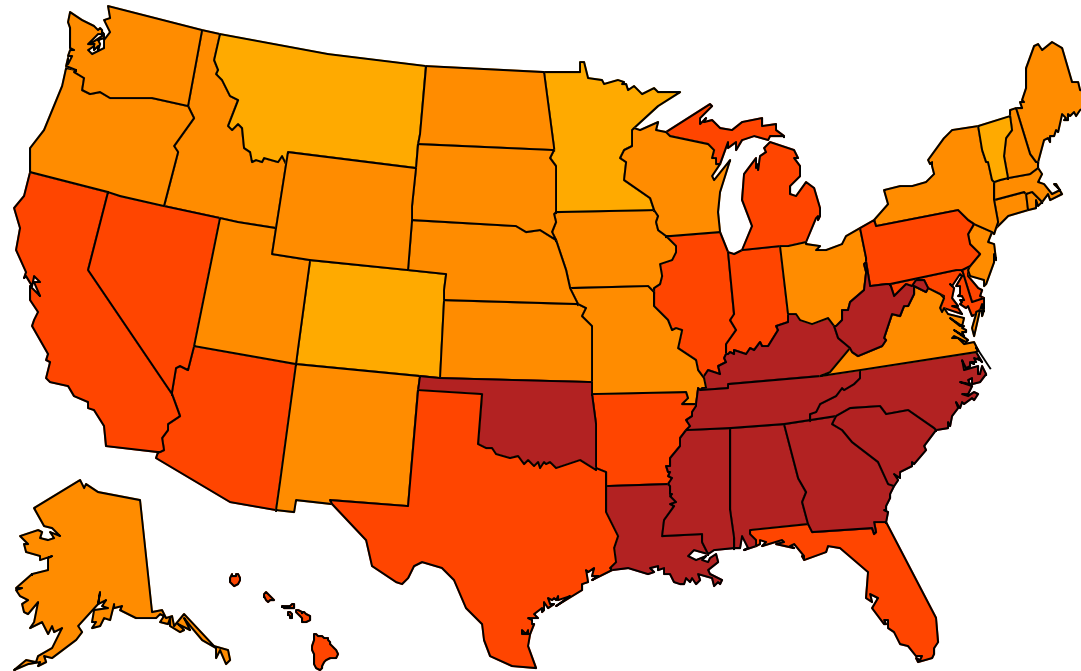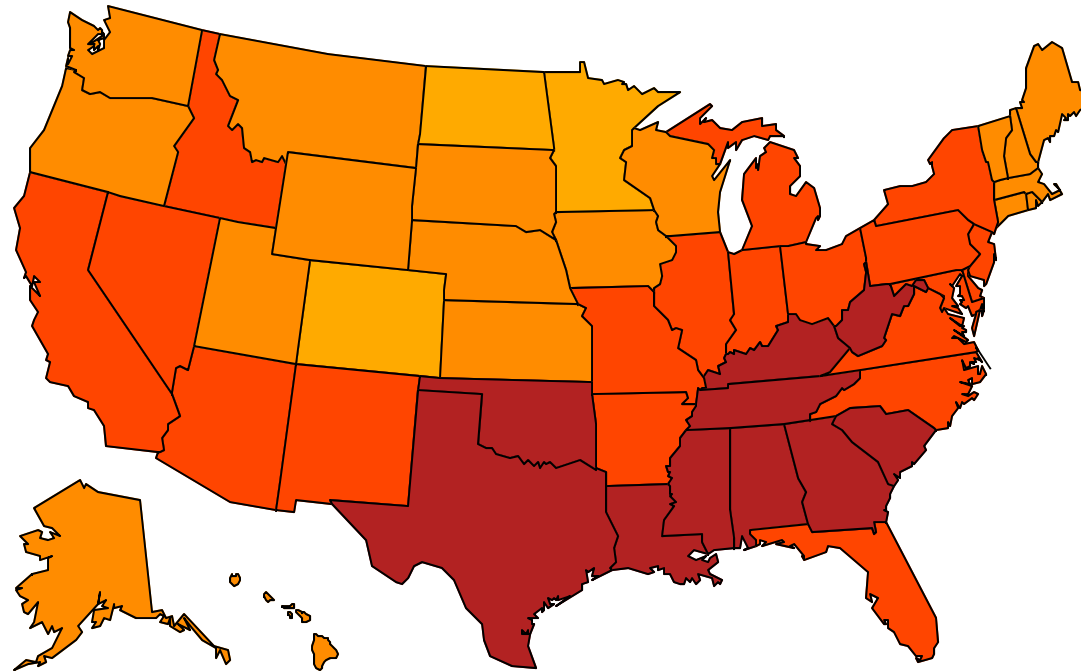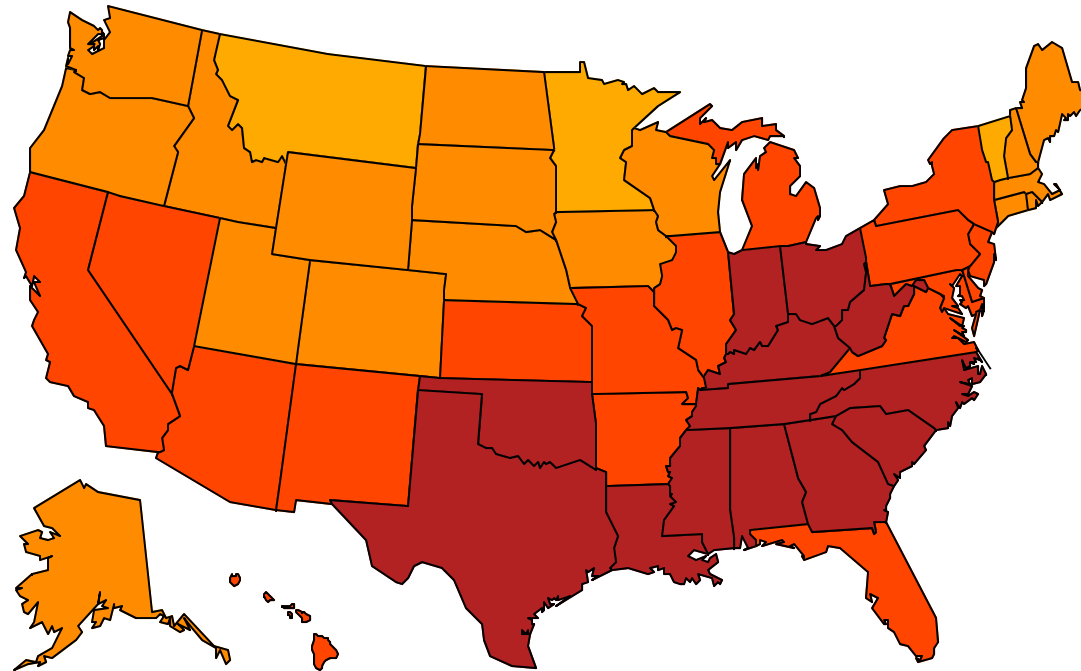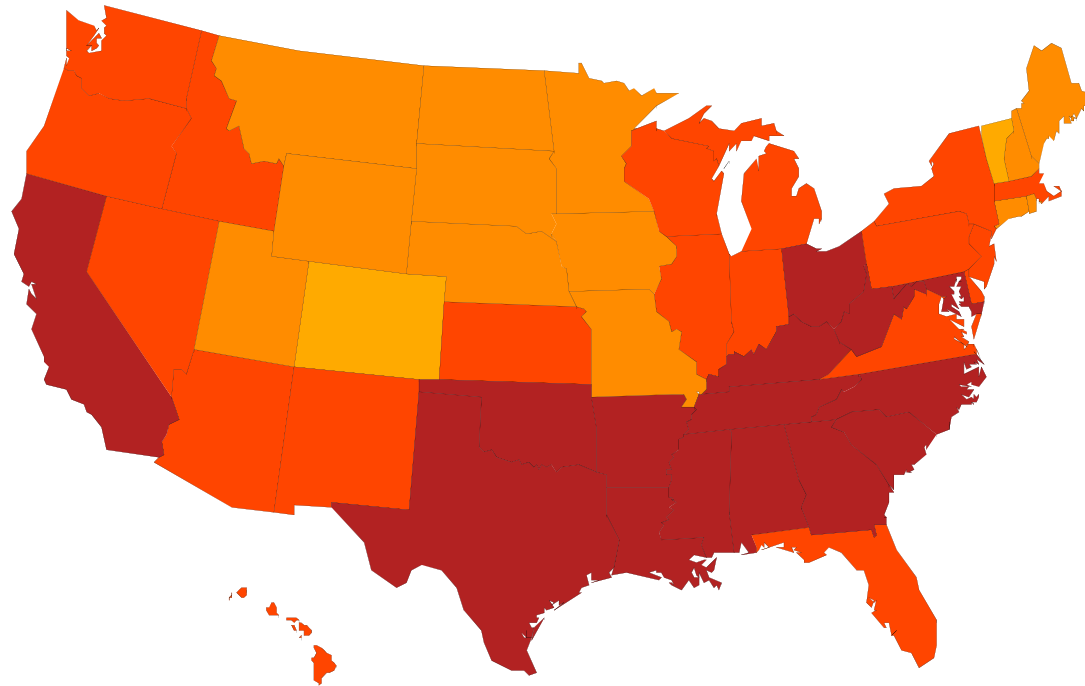
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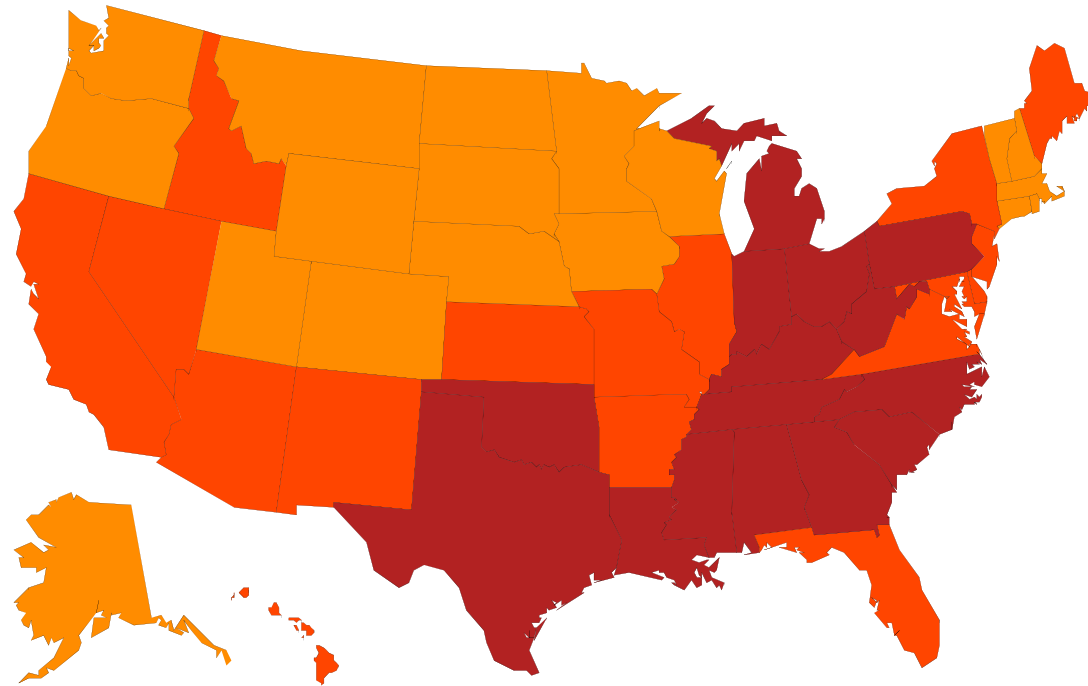
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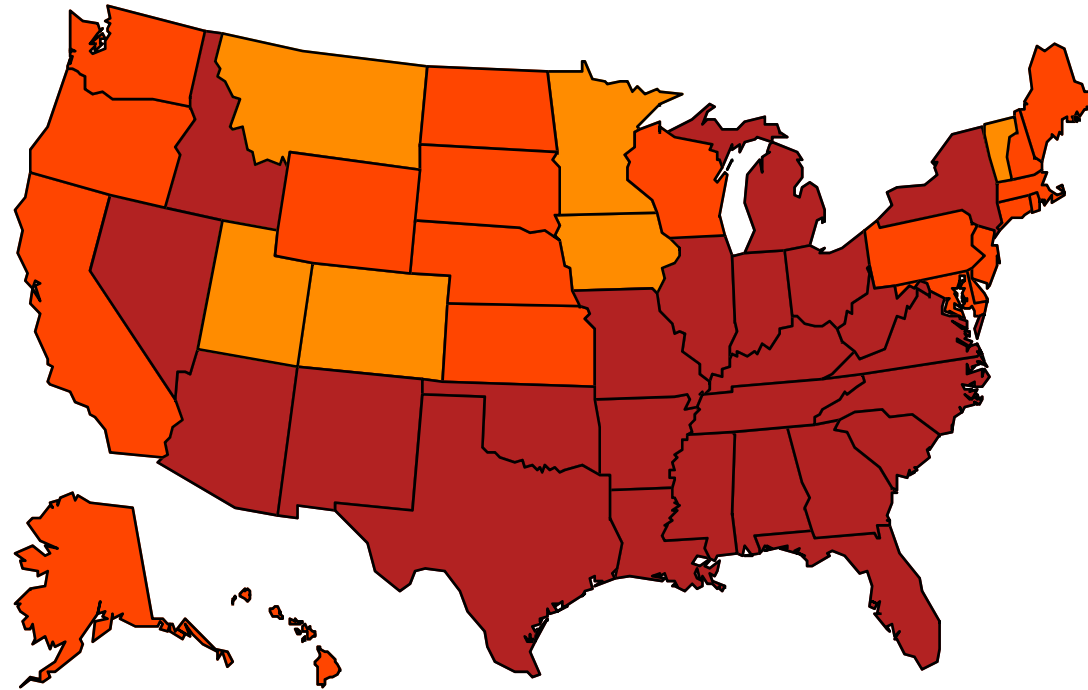
2012
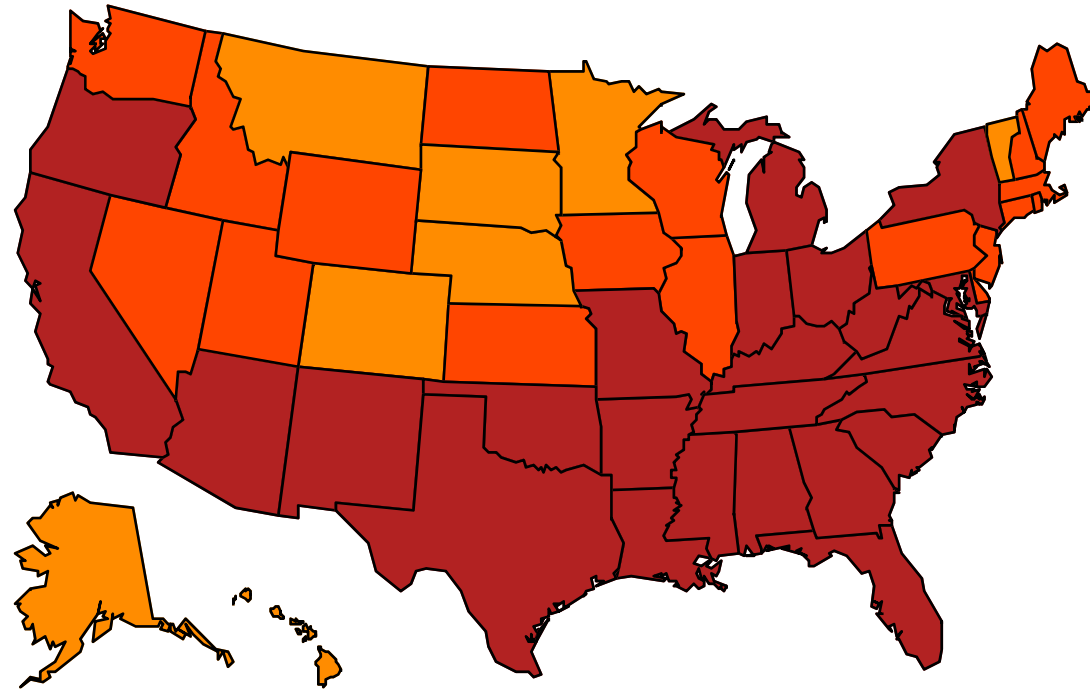
2013
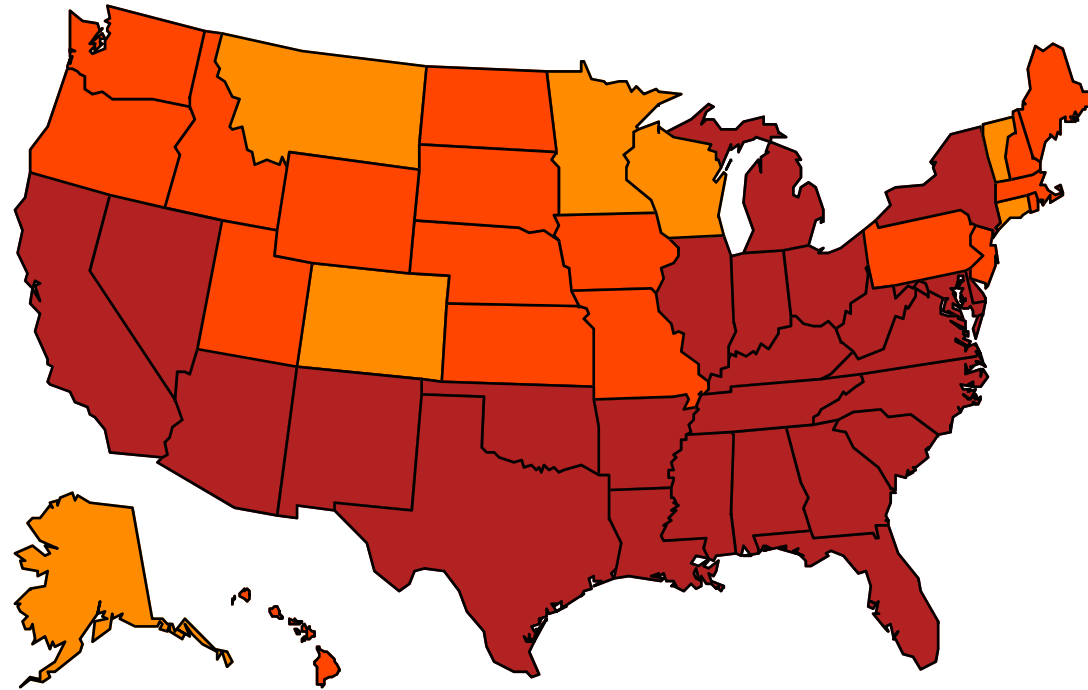
Age-Adjusted Percentage of Adults Diagnosed with Diabetes- 2014
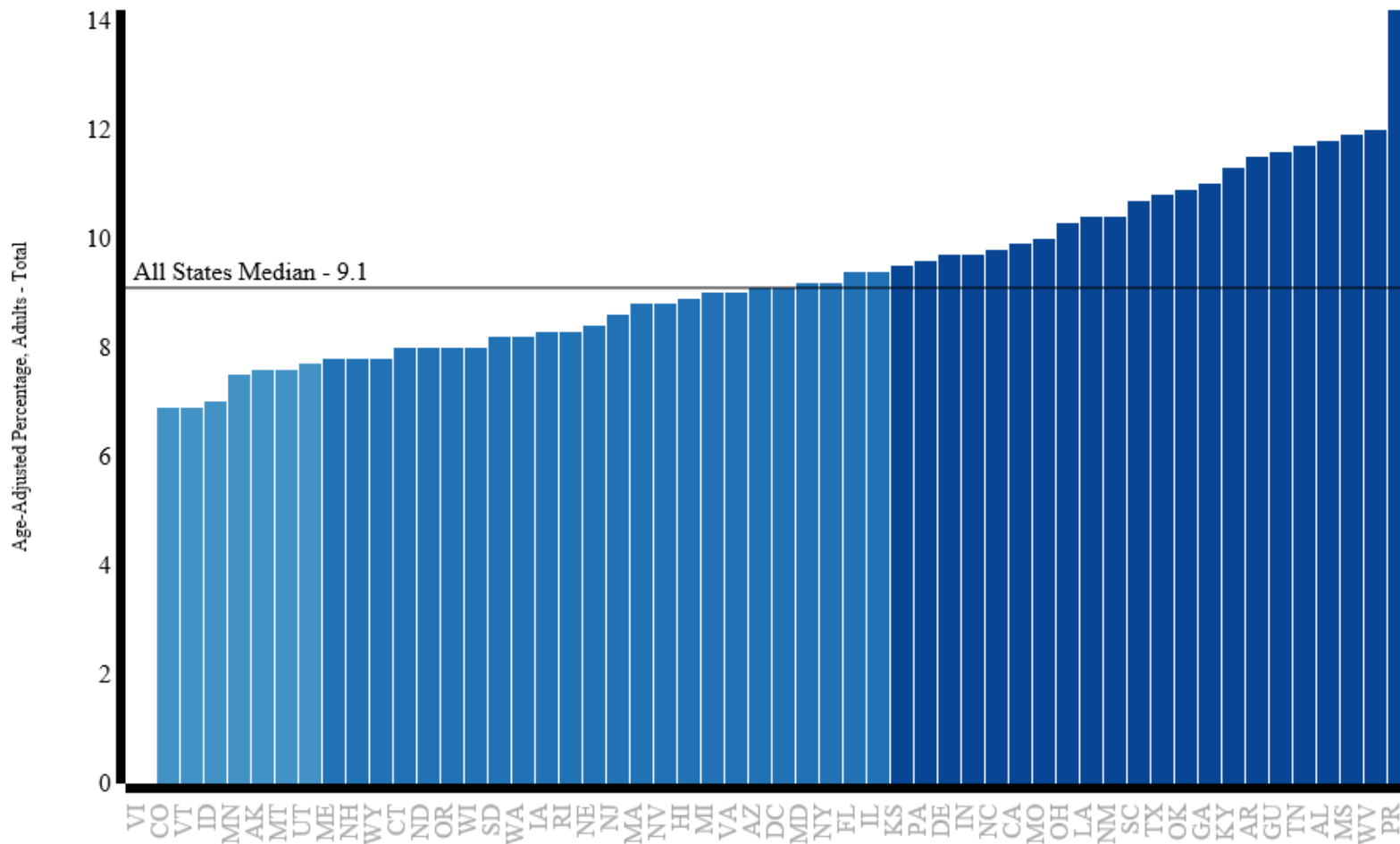
Infections in Diabetics

Why the increased risk of infections?

Susceptibility to Infections in Diabetics:

- Peripheral Neuropathy

- Autonomic Neuropathy

- Hyperglycemia

- Poor tissue perfusion due to peripheral vascular disease

Diabetes Affects the Nerves

Blood vessel — Nerve

Normal

Diseased blood vessels

Nerves shrivel when blood vessels disappear
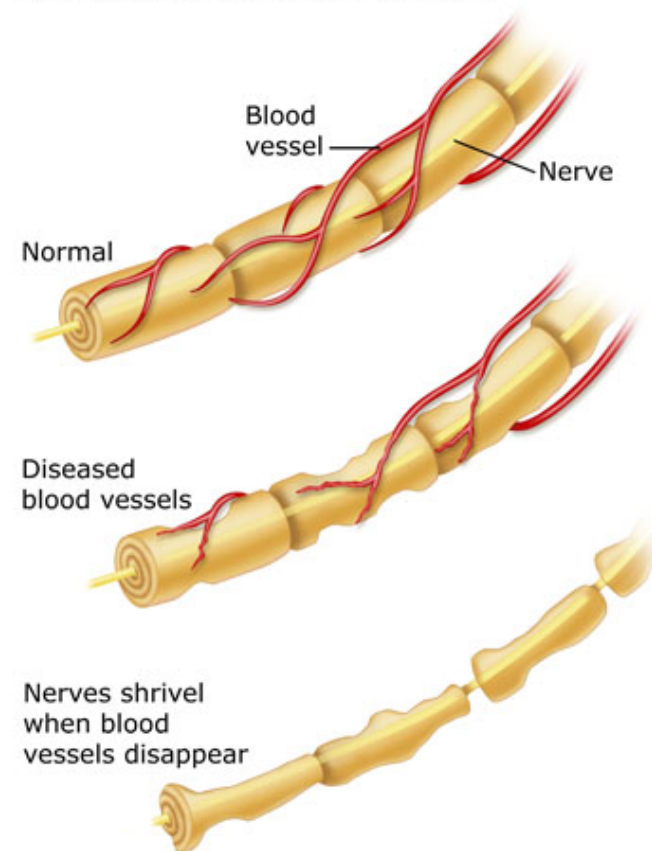
Weintrob AC, Sexton DJ. Susceptibility to infections in persons with diabetes mellitus. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA. 2012.
khardori R. Infection in patients with diabetes mellitus. Medscape reference. WebMD 2011.
http://dtc.ucsf.edu/images/charts/5.d.jpg

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Immunity to
Mycobacterium tuberculosis
in Diabetes

Obesity and Lipotoxicity
Clinical Implications

Liver
- ↑ Insulin resistance
- ↑ HGP
- ↑ VLDL production
- NAFLD→cirrhosis

Dysfunctional adipose tissue
- ↑ Visceral fat
- ↑ Portal FFA→NAFLD
- ↑ Cytokine production
- ↓ Adiponectin

Muscle
- ↓ Mitochondrial function
- ↓ VO$_2$ max
- Insulin resistance
- Sarcopenia?

Atherosclerosis
- Endothelial dysfunction
- Plaque formation
- CV events

Heart
- Impaired energy metabolism
- Diastolic dysfunction
- ↑ Risk of CAD?

Pancreas
- ↑ β-cell apoptosis
- ↓ Insulin secretion
- ↑ T2DM

Cusi K. Gastroenterology 2012, 142:711-25
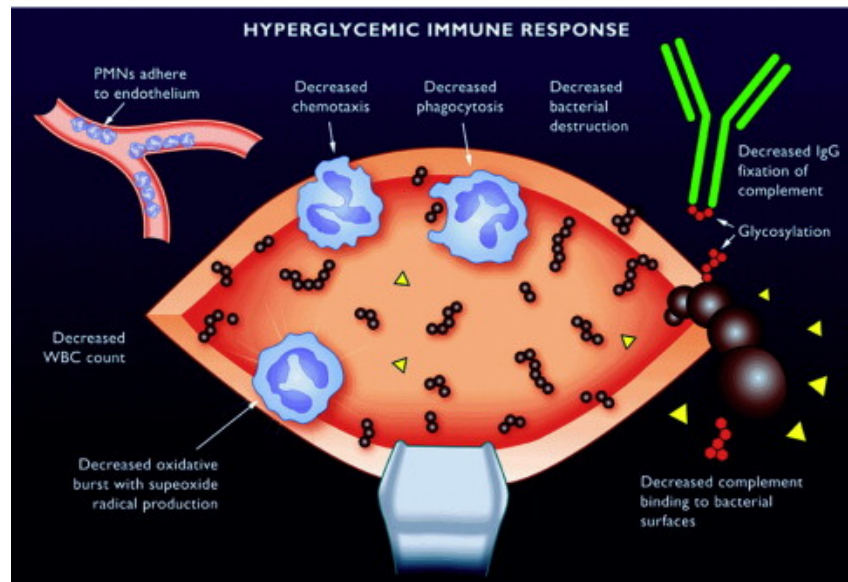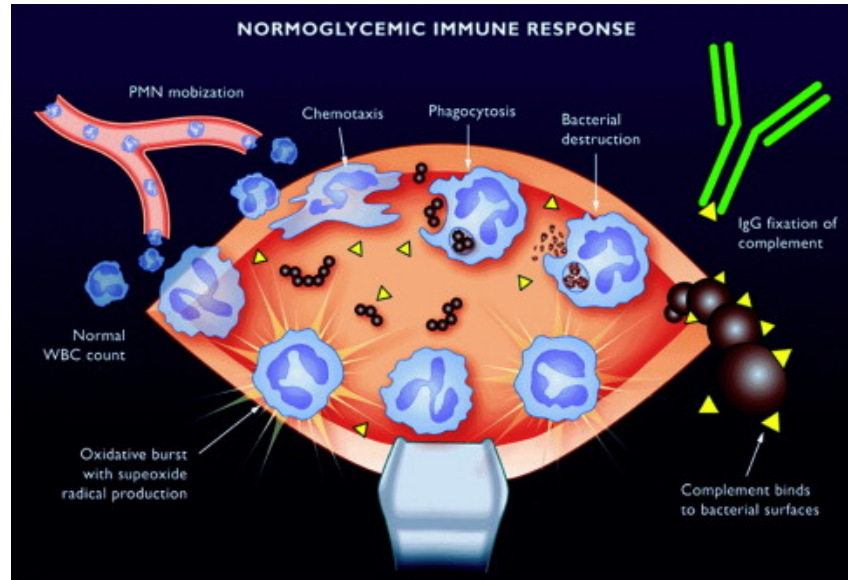
Adapted from Shilling AM, Raphael J. Diabetes, hyperglycemia, and infections. Best Practice & Research Clinical Anaesthesiology. 2008;22(3):519-535. http://ars.sciencedirect.com/content/image/1-s2.0-S1521689608000566-gr3.jpg

Does Diabetes Effect the Risk of Infection and Persistence?

Relative Risk of LTBI in Patients with Diabetic versus Non-Diabetic Patients

- Has not been studied systematically in the last fifty years

- Boucot in 1952 chest x-ray survey found abnormal films suggestive of TB in 8.4% diabetic contacts versus 4.3% of non-diabetics

Bourcot et al. Ann Rev Tuberc 1952

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IGRAs and Diabetes

- The sensitivity of the interferon-gamma release assays (IGRAs) in the detection of Mycobacterium tuberculosis infection or disease may be affected by immune dysregulation in diabetes.

- As millions of type 2 diabetes patients are at risk for tuberculosis (TB) worldwide, it is important to determine if the sensitivity of IGRAs is compromised in this population.

- A prospective cohort study was designed to evaluate the sensitivity of the IGRAs QuantiFERON®-TB Gold (QFT-G) and T-SPOT®.TB among specimens from newly diagnosed adults with microbiologically confirmed TB with and without diabetes.

- Investigators also evaluated the association between QFT-G results and diabetes-associated conditions (dyslipidemia, obesity).

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IGRAs and Diabetes

- QFT-G sensitivity was 70% among TB patients.

- Patients with diabetes, chronic hyperglycemia or overweight/obesity were more than twice as likely to have positive test results in multivariate models (P < 0.05).

- Low high-density lipoprotein cholesterol or high triglycerides were not associated with assay results.

- In a separate group of TB patients (n = 43), T-SPOT.TB was 93% sensitive, with similar performance in patients with and without diabetes.

- CONCLUSION:
  - IGRA sensitivity is not compromised by diabetes in TB patients. Accordingly, IGRAs may also be suitable for diagnosing TB infection in diabetes patients, which is required to assess TB risk.

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What is the impact of diabetes on the risk of progression to active TB?

Risk of Developing Disease
Normal Immune System

- Untreated, 5% of infected persons with normal immunity develop TB in first 1–2 years post infection, another 5% later in life

- Thus, about 10% of infected persons with normal immunity will develop TB at some point in life if not treated

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Association Between Diabetes and Tuberculosis

- Investigators sought to determine the characteristics, prevalence and temporal trends of diabetes in US and foreign-born persons attending the San Francisco Tuberculosis Clinic.

- Investigators analyzed data from patients with the diagnosis of tuberculosis, latent infection, or not infected with Mycobacterium tuberculosis.

- They assessed the temporal trend and the characteristics of individuals with and without diabetes.

- Between 2005 and 2012, there were 4371 (19.0%) individuals without evidence of tuberculosis infection, 17,856 (77.6%) with latent tuberculosis, and 791 (3.4%) with tuberculosis. 66% were born in the United States, China, Mexico, and the Philippines.

Suwanpimolkul G, et.
(2014) PLoS ONE 9(12):

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Association Between Diabetes and Tuberculosis

- The prevalence of diabetes was the highest among individuals with tuberculosis and increased during the study period.

- Patients with tuberculosis and diabetes were more likely to be male, older than 45 years and born in the Philippines.

- There was a disproportionate association of TB and DM relative to LTBI and DM among Filipinos in individuals older than 45 years old.

- CONCLUSIONS:
  - The data suggest that Filipinos older than 45 years old are more likely to have tuberculosis probably due to a higher prevalence of diabetes.
  - In San Francisco, tuberculosis-screening programs in individuals with diabetes and latent tuberculosis may be beneficial in patients older than 45 years old especially from the Philippines.

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Prevalence of DM in the different TB categories in all study subjects: April 2005- March 2012.
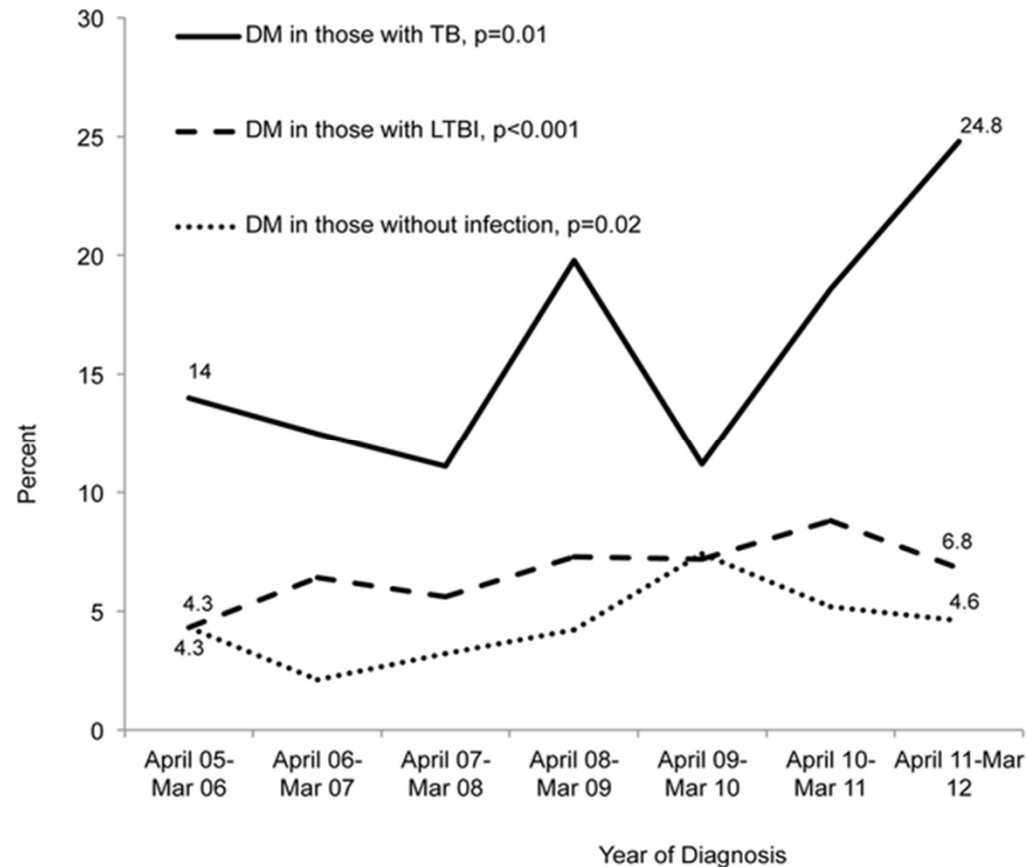
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How strong is the effect of diabetes on the risk of developing tuberculosis?

- In a study from Taiwan, researchers prospectively investigated the risk of tuberculosis among persons with diabetes stratified by severity.

- The prospective cohort study involved 17 715 Taiwanese persons on whom baseline data were collected during Taiwan's 2001 National Health Interview Survey.

- Participants' subsequent care was captured from the National Health Insurance database.

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How strong is the effect of diabetes on the risk of developing tuberculosis?

- Diabetes was significantly associated with tuberculosis (adjusted hazard ratio, 2.09 [95% confidence interval {CI}, 1.10–3.95] and 2.60 [95% CI, 1.34–5.03], respectively).

- Compared with persons without treated diabetes, participants' risk of tuberculosis increased as the number of complications of diabetes mellitus increased (P = .0016), with >3-fold risk among those with ≥2 diabetes-related complications (odds ratio, 3.45; 95% CI, 1.59–7.50).

- Similarly, the risk increased among those with higher Diabetes Complications Severity Index scores (P = .0002).

- **Conclusions.** The risk of developing tuberculosis increased among those with increasing diabetes severity.

Baker et al Clin Infect Dis. (2012)
54 (6): 818-825

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Clinical Characteristics of TB Associated with Diabetes

- Investigators from Spain sought to analyze the prevalence of DM and its associated factors among adults with TB in a large city in an industrialized country.

- A population-based study in adults diagnosed with TB between 2000 and 2013 in Barcelona.

- They studied potentially associated sociodemographic and clinical/epidemiological factors.

- Logistic regression was used to calculate odds ratios (ORs) and their 95% confidence intervals (CIs).

- Of 5849 TB patients, 349 (5.9%) had DM.

- The annual prevalence of DM ranged from 4.0% to 7.2%.

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Clinical Characteristics of TB Associated with Diabetes

- Factors associated with DM were:
    - being Spanish-born (OR 1.46, 95%CI 1.11-1.96),
    - age ⩾40 years (OR 6.08, 95%CI 4.36-8.66),
    - cavitary patterns on chest X-ray (OR 1.42, 95%CI 1.08-1.86),
    - experiencing more side effects due to anti-tuberculosis treatment (OR 1.86, 95%CI 1.28-2.64)
    - and hospitalization at the time of diagnosis (OR 1.8, 95%CI 1.40-2.31).
- Human immunodeficiency virus infection was associated with a lower probability of DM in both subjects with a history of injection drug use (OR 0.27, 95%CI 0.10-0.57) and those without (OR 0.04, 95%CI 0.002-0.19).
- CONCLUSIONS: DM prevalence among adults with TB in Barcelona is low and remained stable over the 14-year study period. However, TB patients with DM were potentially more infectious and their clinical management was more complicated.

Moreno Martinez et al Int J Tuberc Lung Dis. 2015 Dec;19(12):1507-12

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Do chest radiographs appear differently in diabetic TB patients?

- To assess radiological images of pulmonary tuberculosis in a large population of diabetic patients.

- Radiographs from in-patients admitted with pulmonary tuberculosis and diabetes (TBDM group, n = 192) were reviewed and compared with a control group of patients with pulmonary tuberculosis alone (TB group, n = 130).

- Both TB patients with DM and those without DM had a similar evolution time of tuberculosis (approximately 2 years).

- Statistical differences were observed as follows: TBDM patients were older (51.3+/-0.9 vs. TB group 44.9+/-1.8 years, mean +/-SEM), and had a decreased frequency of upper (17% vs. 56%), and an increased frequency of lower (19% vs. 7%) and upper + lower (64% vs. 36%) lung field lesions.

Perez-Guzman et al Int J Tuberc Lung Dis. 2001 May;5(5):455-61.

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Do chest radiographs appear differently in diabetic TB patients?

- More TBDM patients developed:
  - cavitations (82% vs. 59%)
  - more often in the lower lung fields (29% vs. 3%)
  - more multiple cavities were seen in TBDM patients (25% vs. 2%).
  - had a lower total leukocyte count (8836.7+/-219.5 vs. 10013.1+/-345.2 cells/mm3), mainly due to a lower number of non-lymphocyte cells (6815.8+/-221.8 vs. 8095.7+/-321.9 cells/mm3).
- Multiple logistic regression showed that being a diabetic patient was the most important factor determining lower lung field lesions and cavities.
- CONCLUSIONS: This study in a large number of diabetics with pulmonary tuberculosis confirmed that their chest X-ray images significantly depart from the typical presentation. Clinicians must keep this in mind to avoid misdiagnosis.

Perez-Guzman et al Int J Tuberc Lung Dis. 2001 May;5(5):455-61.

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Clinical and Radiographic Features of TB Associated with Diabetes

- Investigators sought to study the clinical and radiological features of lower lung field tuberculosis (LLFTB) in relation to the patients of nonlower lung field tuberculosis (non-LLFTB) in India.

- All the patients of lower lung field tuberculosis defined by the lesions below an arbitrary line across the hila in their chest X-rays were included in the study.

- Their sputum for acid fast bacilli, HIV, blood sugar, and other relevant investigations were performed..

Singh et al J Trop Med.
2015;2015:230720

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Clinical and Radiographic Features of TB Associated with Diabetes

- 2136 cases of pulmonary tuberculosis were studied.

- Among them 215 (10%) cases of patients were diagnosed as the case of lower lung field tuberculosis.

- Females (62%) were more commonly affected.

- The relative risk of having the LLFTB in diabetes patients, HIV seropositive patients, end stage renal disease patients, and patients on corticosteroid therapy was high.

- In diabetes the relative risk (RR) was 4.95 similar to that found in HIV (5.17)

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Attributable risk of TB from Diabetes > HIV in Texas/Mexico border

TB suspects ≥ 20 years of age ($n = 333$)

Participants excluded due to missing data:
TB ruled out ($n = 41$)
MOTT ($n = 14$)
Missing data required for TB or inconclusive TB[a] diagnosis ($n = 41$)
Missing information required for diabetes classification[b] ($n = 4$)

Total TB cases for analysis ($n = 233$)
South Texas ($n = 61$); North-eastern Mexico ($n = 172$)
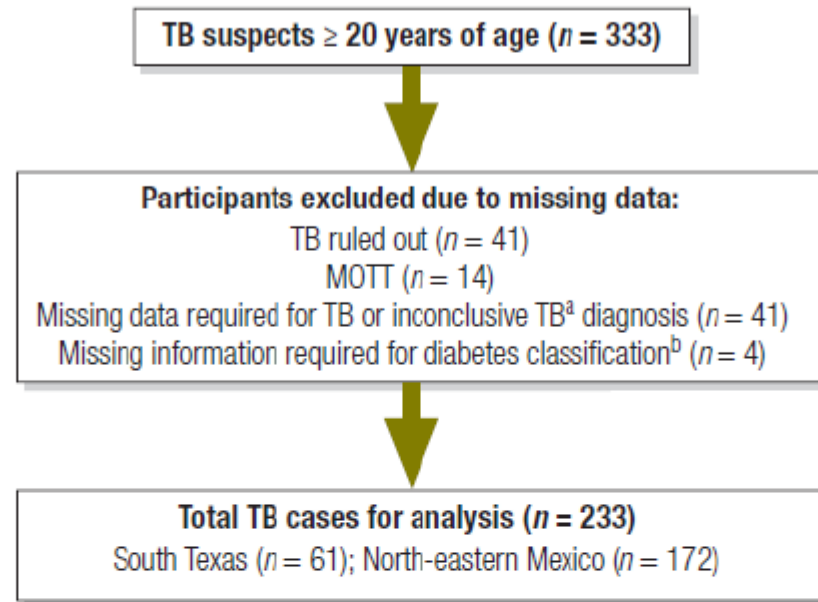
Age (years)	Diabetes			HIV infection		
	RR (95% CI)	$AR_{exposed}$ (%)[a]	$AR_{population}$ (%)[b]	RR (95% CI)	$AR_{exposed}$ (%)[a]	$AR_{population}$ (%)[b]
South Texas						
20+ ($n=61$)	2.7 (1.6–4.4)	63	26	17.8 (6.5–9.0)	94	5
20–34 ($n=20$)	0.9 (0.1–6.8)	−9	1	34.4 (8.0–147.7)	97	6
35–64 ($n=32$)	5.1 (2.6–10.2)	80	48	12.2 (2.9–50.9)	92	5
65+ ($n=9$)	1.7 (0.5–5.8)	41	22	0[c]	NA	NA
NE Mexico						
20+ ($n=172$)	3.1 (2.3–4.2)	68	24	16.0 (7.5–34.0)	94	3

Restrepo et al. *Bull WHO* 2011

Screening for diabetes in new TB patients can be highly effective (India)

Type of TB	Number of TB patients whose DM status was ascertained [a]	Number with previously known DM [b]	Number of DM newly diagnosed [c]	Additional Yield [c/(b+c)*100]	Number needed to screen (NNS) [(a−b)/c]
New Smear Positive Pulmonary TB	307	87	70	45%	3.1
New Smear Negative Pulmonary TB	37	4	7	64%	4.7
New Extra-pulmonary TB	128	15	21	58%	5.3
Relapse	35	12	8	40%	3.3
Treatment after Failure	19	7	2	22%	6.0
Treatment after Default	26	3	7	70%	3.3

Overall, number of **TB patients needed to screen** (with HbA1c) in order **to detect one new case of diabetes was just 4**.

Balakrishnan et al. *PLoS ONE* 2012

Does diabetes treatment effect treatment outcomes?

Clinical Outcomes in TB Associated with Diabetes

- Investigators sought to determine the clinical consequences of pulmonary tuberculosis (TB) among patients with diabetes mellitus (DM).

- They conducted a prospective study of patients with TB in Southern Mexico.

- From 1995 to 2010, patients with acid-fast bacilli or *Mycobacterium tuberculosis* in sputum samples underwent epidemiological, clinical and microbiological evaluation.

- Annual follow-ups were performed to ascertain treatment outcome, recurrence, relapse and reinfection.
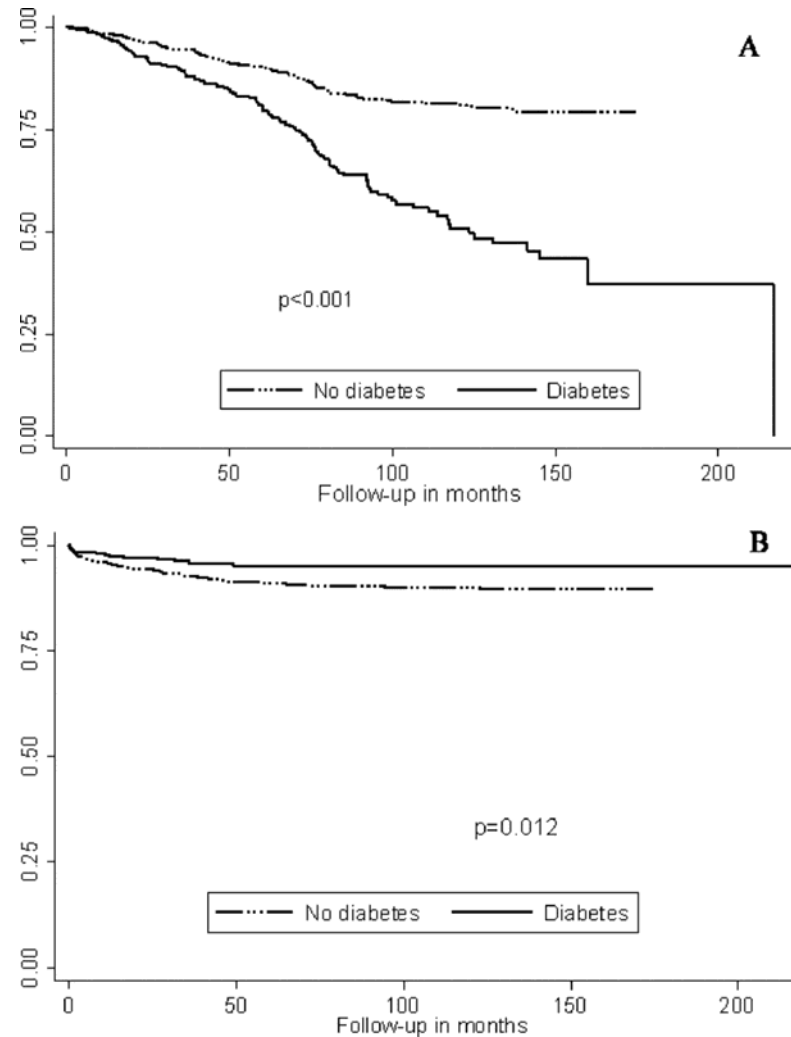
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Clinical Outcomes in TB Associated with Diabetes

- The prevalence of DM among 1262 patients with pulmonary TB was 29.63% (n=374).

- Patients with DM and pulmonary TB had:
  - more severe clinical manifestations (cavities of any size on the chest x-ray, adjusted OR (aOR) 1.80, 95% CI 1.35 to 2.41),
  - delayed sputum conversion (aOR 1.51, 95% CI 1.09 to 2.10),
  - a higher probability of treatment failure (aOR 2.93, 95% CI 1.18 to 7.23),
  - recurrence (adjusted HR (aHR) 1.76, 95% CI 1.11 to 2.79) and relapse (aHR 1.83, 95% CI 1.04 to 3.23).

- Most of the second episodes among patients with DM were caused by bacteria with the same genotype but, in 5/26 instances (19.23%), reinfection with a different strain occurred.

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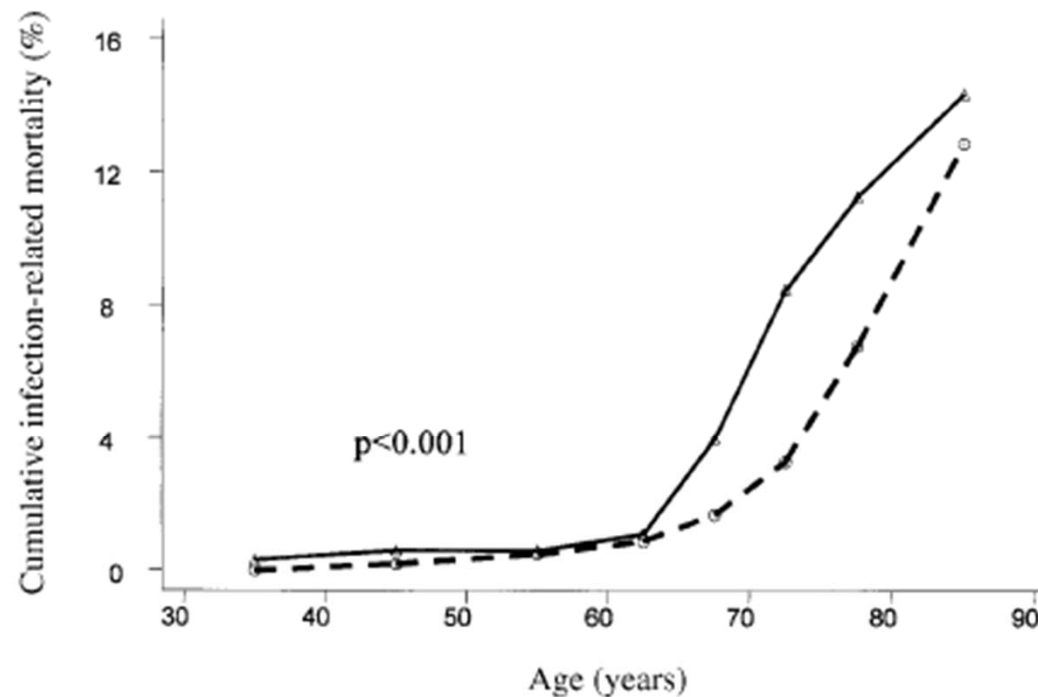# Kaplan–Meier survival curves by diagnosis of diabetes.

María Eugenia Jiménez-Corona et al. Thorax
doi:10.1136/thoraxjnl-2012-201756

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THORAX

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Mortality due to Infections in Diabetics

Figure 1—*Cumulative mortality related to infectious diseases in 9,208 adults by age at follow-up and diabetes status at baseline (solid line, individuals with diabetes; dashed line, nondiabetic individuals). Data for life-table calculations were based on weighted estimates to account for the complex sampling design of NHANES II and thus provide nationally representative estimates. A log-rank test was used to compare the mortality curve.*

Bertoni AG, Saydah S, Brancati FL. Diabetes and the risk of infection-related mortality in the U.S. *Diabetes Care*. 2001;24:1044-1049.

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Risk of TB relapse for TB patients with diabetes compared with TB patients without diabetes
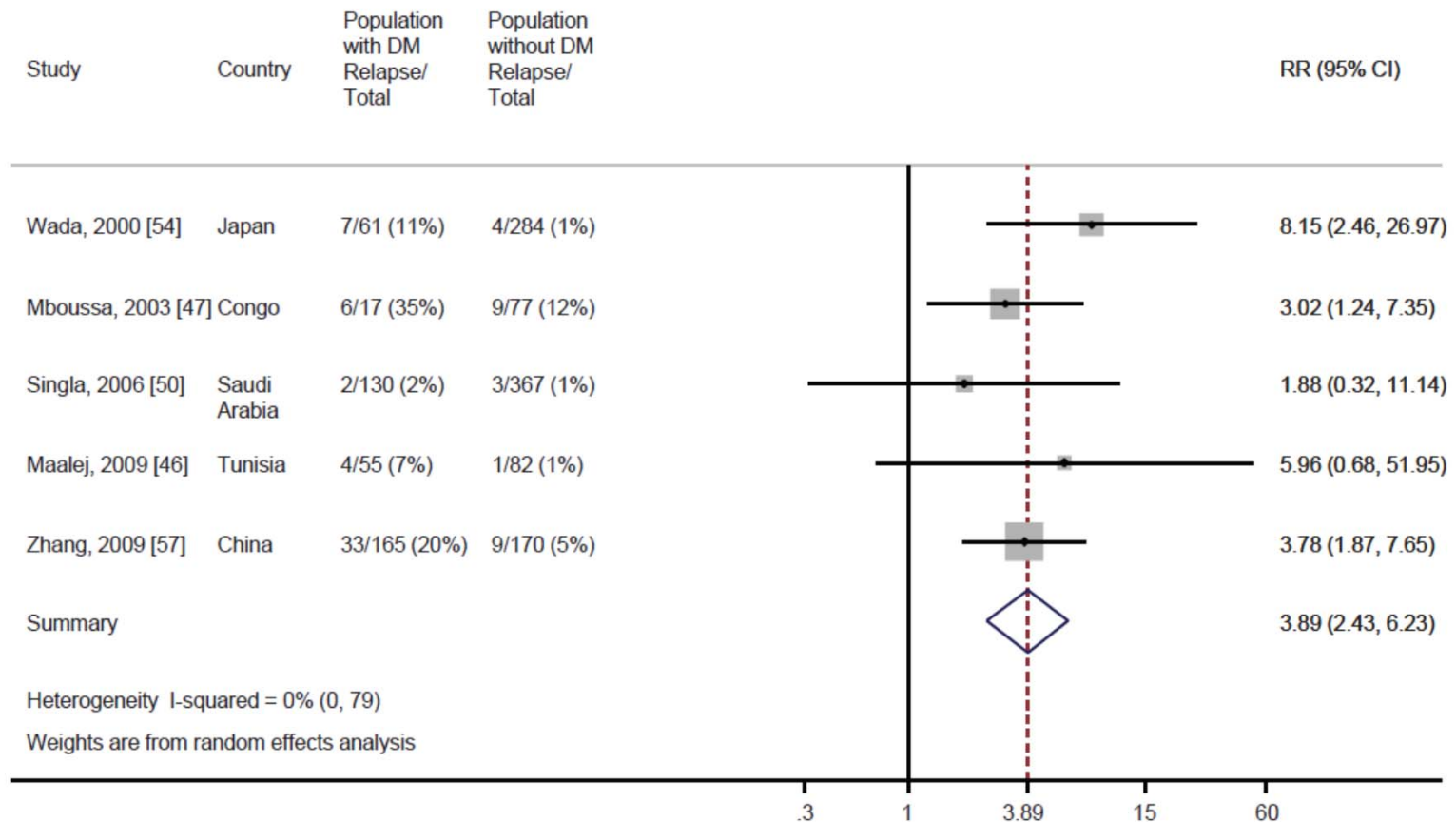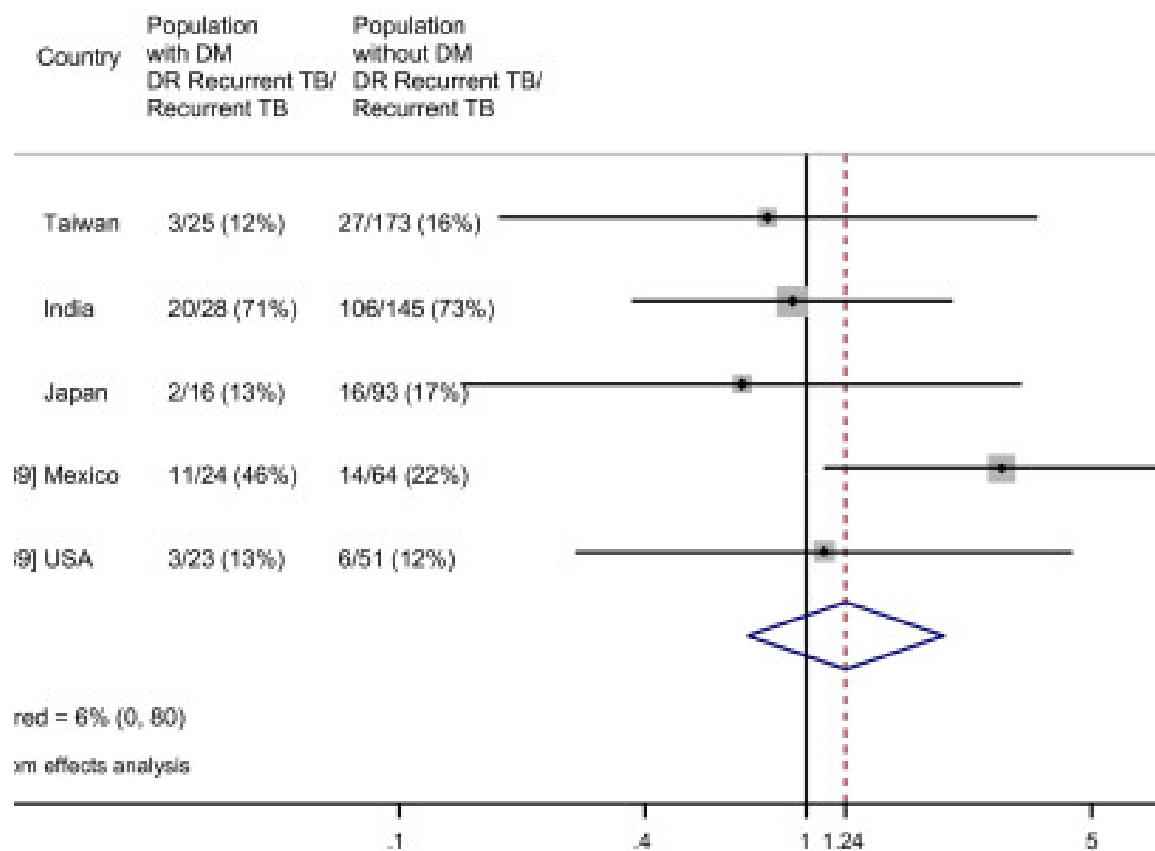
Odds of recurrent TB that is DR, comparing patients with DM to patients without DM. Size of the square is proportional to the precision of the study-specific effect estimates, and the bars indicate the corresponding 95% CIs. The diamond is centered on the summary OR of the observational studies, and the width indicates the corresponding 95% CI.

BMC Med. 2011; 9: 81.

Question

- Which x-ray is more likely to be from a patient that has diabetes?
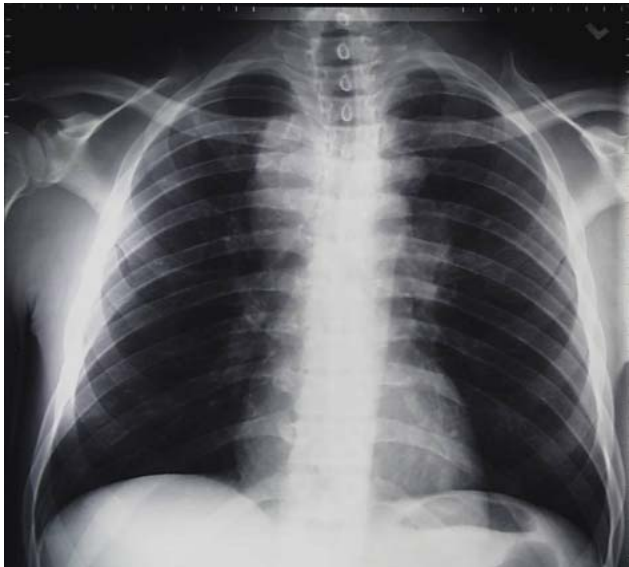
X-ray 1 Mediastinal adenopathy
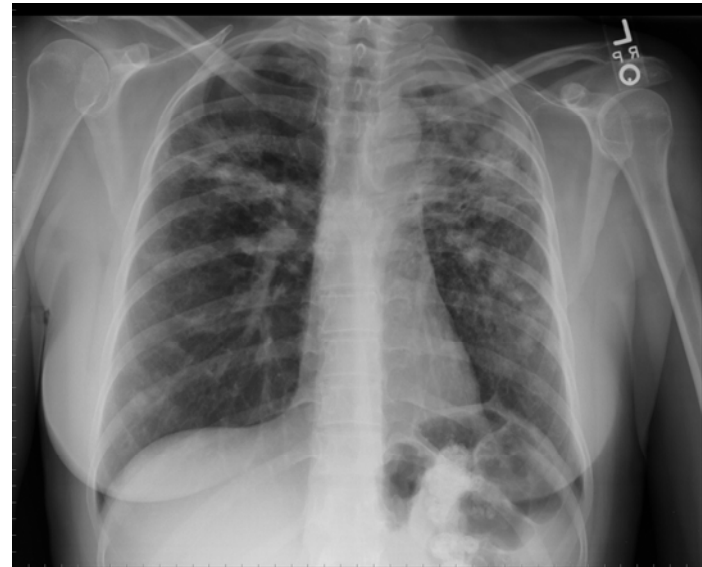
X-ray 2 Upper lobe Infiltrates

Is extra-pulmonary disease more likely as it is in other immunosuppressed patients?

Tuberculosis of the Spine

#027-T.CL.
5/23/01

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Is diabetes related tuberculosis more infectious than non-diabetes related tuberculosis?

Probability TB Will Be Transmitted

- Susceptibility of the exposed person
- Infectiousness of person with TB (i.e., number of bacilli TB patient expels into the air)
- Environmental factors that affect the concentration of *M. tb* organisms
- Proximity, frequency, and duration of exposure (e.g., close contacts)
- Can be transmitted from children, though less likely

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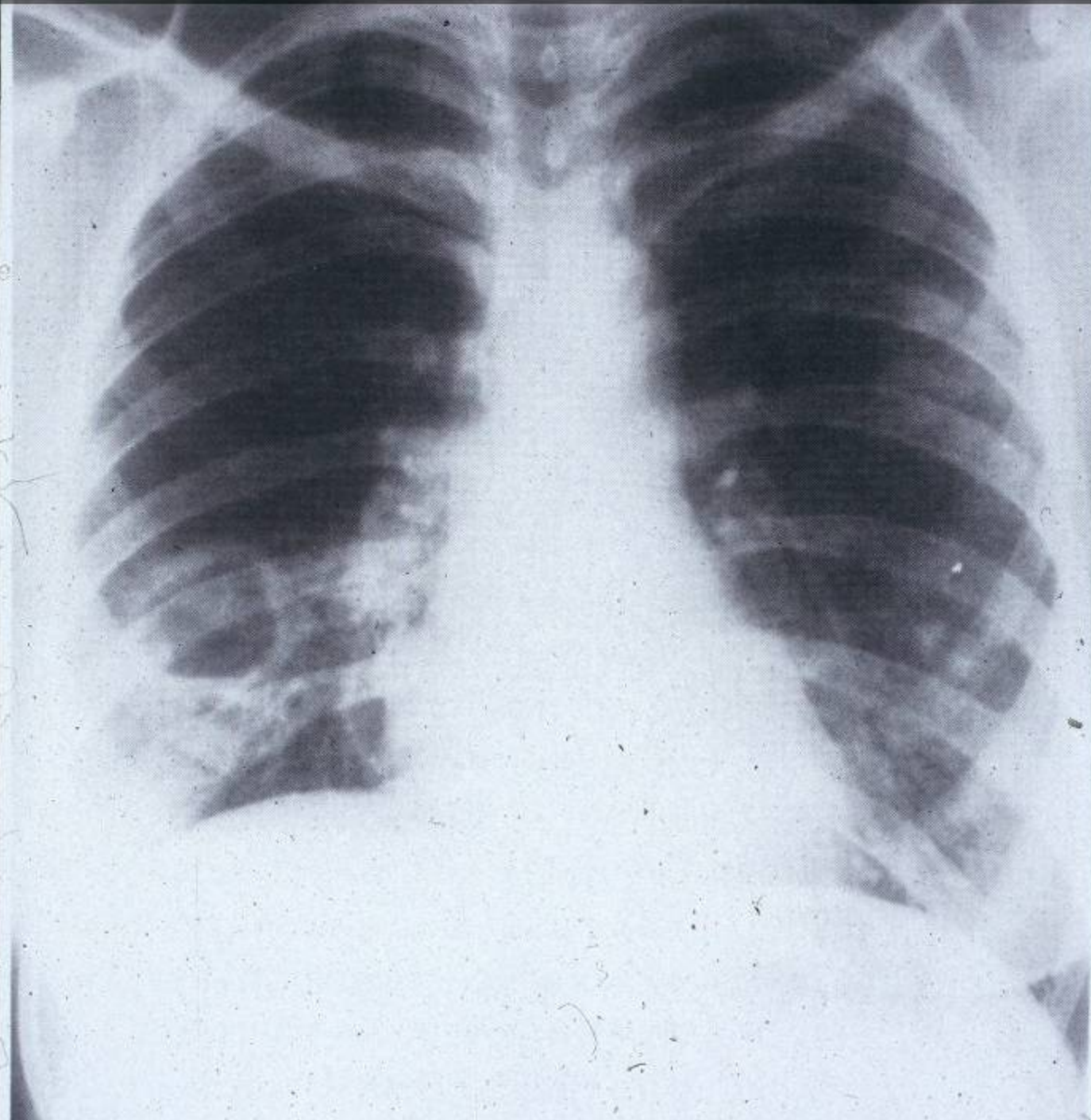
There are no incurable diseases — only the lack of will.

Avicenna